Citation:

König A, Bouzan C, Cohen JT, Connor WE, Kris-Etherton PM, Gray GM, Lawrence RS, Savitz DA, Teutsch SM. A quantitative analysis of fish consumption and coronary heart disease mortality. *Am J Prev Med.* Nov 2005; 29 (4): 335-346.

PubMed ID: 16242600

Study Design:

Meta-analysis or Systematic Review

Class:

M - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

- To quantify the net impact of resulting hypothetical changes in fish consumption across the population
- This work estimates the impact of fish consumption on coronary heart disease (CHD) mortality and non-fatal myocardial infarction (MI)
- Further analyses quantify stroke risk and the impacts of both prenatal methyl mercury (MeHg) exposure and maternal intake of omega-3 polyunsaturated fatty acids (n-3 PUFAs) on cognitive development.

Inclusion Criteria:

- Studies for inclusion in this review were identified by starting with those identified in a previous review. In that review, abstracts were identified by searching Medline, Embase and the Cochrane Central Register of Controlled Trials (4th quarter, 2002).
- From this initial selection of articles the following were included because:
  - The analyses were more recent (i.e., additional follow-up)
  - They were full cohort analyses over nested case-control evaluations
  - The analyses measured exposure in terms of total fish consumption (rather than some subset of fish, such as lean or fatty fish)
  - The analyses controlled for a greater number of potential confounders are also favored.

Exclusion Criteria:

Articles were eliminated from initial review because:

- They followed inappropriate or pediatric populations (subjects aged <19 years)
- They did not mention n-3 PUFA intake

- They involved n-3 PUFA intake exceeding 6g per day
- They were prospective interventions of less than four weeks in duration
- They did not report outcomes of interest
- They reported only n-3 PUFA tissue levels but not intake rates
- RCTs were omitted if follow-up was <12 months.

From this initial selection, further limitations reduced the number of articles because:

- They reported relative risks for non-fatal MI or CHD-related mortality (corresponding to the sum of the risks for fatal MI and sudden cardiac death)
- They quantified risk relative to a no intake or very low intake reference group (fish consumption of less than one fish serving per month)
- They followed subjects approximately representative of the general population in terms of CHD risk factors (i.e., we omitted studies that limited attention to populations with particular important risk factors, such as smokers or populations with protective characteristics, such as vegetarians)
- They had a study design rated by Wang et al, 19 as either "A" (least bias; results are valid) or "B" (susceptible to some bias, but not sufficient to invalidate the results), but not "C" (significant bias that may invalidate the results)
- They evaluated the impact of either fish consumption or dietary supplements containing PUFAs found in fish (eicosapentaenoic acid [EPA] or docosahexaenoic acid [DHA], rather than precursors for those compounds).

Description of Study Protocol:

Search Procedures

Authors searched articles using:

- Medline database
- The articles selected in a recent literature review that used Medline, Embase and the Cochrane Central Register of Controlled Trials
- An expert panel to identify studies.

Study Quality Assessment

Authors relied on the quality assessment of the previous *Evidence Report*.

Authors did further qualify studies for selection based on:

- Reported relative risks (RR) for non-fatal MI or CHD-related mortality (corresponding to the sum of the risks for fatal MI and sudden cardiac death)
- Quantified risk relative to a no intake or very low intake reference group (fish consumption of less than one fish serving per month)
- Followed subjects approximately representative of the general population in terms of CHD risk factors (i.e., we omitted studies that limited attention to populations with particular important risk factors, such as smokers or populations with protective characteristics, such as vegetarians)
- Had a study design rated by Wang et al. 19 as either "A" (least bias; results are valid) or "B" (susceptible to some bias, but not sufficient to invalidate the results), but not "C" (significant bias that may invalidate the results)
- Evaluated the impact of either fish consumption or dietary supplements containing PUFAs

found in fish (EPA or DHA, rather than precursors for those compounds)
- Double counting information was avoided. Attention was limited to a single set of results favoring:
    - Analyses that are more recent (i.e., additional follow-up)
    - Full cohort analyses over nested case-control evaluations
    - Analyses that measure exposure in terms of total fish consumption (rather than some subset of fish, such as lean or fatty fish)
    - Analyses that controlled for a greater number of potential confounders are also favored.

Relationships Investigated

- Authors included observational studies on fish consumption and randomized controlled trials (RCTs) of n-3 PUFA intake to quantify the relationship between:
    - Fish consumption (servings per week) and CHD-event relative risk in individuals with no pre-existing CHD
    - N-3 intake (g per day) and CHD-event relative risk in individuals who do have pre-existing CHD.
- RCTs included for review evaluated the secondary prevention of CHD (i.e., they followed subjects who did have pre-existing CHD).
- Populations included:
    - Adult men and women older than 19 years
    - With and without evidence of CHD.

Data Collection Summary:

Information abstracted from articles

Authors developed a dose-response relationship between the RR of various cardiovascular outcomes (CHD and non-fatal MI) and either n-3 intake or fish consumption (servings per week).

Data combination

- The results from each of the relevant studies were first combined into a single data set. For example, to quantify the relationship between fish consumption and the risk of nonfatal MIs in individuals with no pre-existing CHD, the analysis combines the 12 non-reference group, RR values from the Ascherio et al., Hu et al., and Mozaffarian et al. studies. These observations, weighted by their statistical precision, are then regressed against fish consumption (servings per week)
- In addition, for studies reporting exposure in terms of fish consumption, this analysis converts consumption rates expressed as ranges (e.g., “one to three fish servings per month”) into point estimates expressed as average fish consumption servings per week. When lower and upper bounds are specified for a range, the range’s mid-point is used (two fish servings per month in the preceding example, amounting to around 0.5 servings per week). If no upper bound is specified (e.g., “five or more servings per week”), the upper bound value is assumed to be seven fish servings per week. For studies that express fish consumption in terms of grams per day, it is assumed that 100g of fish is equivalent to one serving. This assumption is consistent with US EPA estimates 56. The RCTs of individuals with pre-existing CHD report n-3 PUFA intake in grams per day, which is used as the independent variable in a separate regression analysis.

Analytic Methods Used

- Observations of CHD risk or MI risk (y axes) were weighed by their statistical precision and then regressed against fish consumption in servings per week (x axes)
- Regression analysis assumed that statistical precision is inversely proportional to the squared width of the log-transformed, RR confidence interval (CI). That measure of precision was used because the parameter estimates in a logistic regression are normally distributed after log transformation. Hence, the width of the log-transformed CI is proportional to the estimate's standard error, and the square of the width is proportional to the estimate's variance. The variance, in turn, is inversely proportional to the weight assigned an observation when aggregating data for a meta-analysis
- This analysis uses regression of aggregate CHD risk (sudden death plus fatal MI) against fish consumption to investigate the plausibility of the dose-response relationships implied by these two mechanisms. For example, for the CHD mortality risk analysis, a finding that the intercept term is distinct from zero (i.e., its distribution of plausible values is not centered on zero) supports the hypothesis that any level of fish consumption confers protection against this risk compared to eating no fish. A finding that the coefficient for the linear term is distinct from zero supports the hypothesis that further consumption of fish confers incremental protection against this risk. Finally, a sensitivity analysis adds a quadratic term to the linear regression. The quadratic term allows the regression to approximate the dose-response relationship if incremental benefits decrease at higher levels ofn-3 intake or fish consumption.

Description of Actual Data Sample:

Number of Articles Included from Articles Identified

- Initial review=39 articles
- Included in review=11 articles.

Number and Type of Studies Reviewed

- Observational studies; seven
- RCTs; four.

Studies Involving Subjects with No CHD at Baseline (abbreviated)

Study (Year)	Population	Population Country	Follow-up (Years and Person-years)
Kromhout (1985)	872 men aged 40-59 years with no CHD at baseline	Netherlands	20[c]
Ascherio (1995)	44,895 male health workers, no known CHD at baseline	US	6 242,029
Daviglus (1997)	1,822 males free of CVD at baseline	US	30 47,153
Albert (1998)	20,551 male physicians with no MI, cerebrovascular disease, or cancer at baseline	US	11 253,777
Oomen (2000)	1,097 males aged 50-69[d] free of CHD at baseline	Italy	20

Hu (2002)	84,688 female nurses with no cancer, angina, MI or CVD at baseline	US	16 1,307,157
Mozaffarian (2003)	3,910 Medicare enrollees with no known CVD at baseline	US	11 approximately 36,400

CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction.

[a] Study does not specify total years of follow-up.
[b] Estimated as the midpoint of the lower and upper ends of the range provided in the original study. If only a lower bound is provided, it is assumed the upper bound is seven servings per week. If the original study expressed fish consumption in grams, it is assumed that one serving is 100g.
[c] Total years of follow-up not specified.
[d] This analysis omits 553 Dutch subjects from consideration because they were part of the Kromhout et al. study. This analysis also omits 1,088 Finns because there was no zero-consumption reference group. The lowest consumption group was zero to 19g per day.

Studies With Subjects Having Pre-existing CHD at Baseline

Study (Year)	Intervention	Assumed n-3 Intake for Treatment Group (g per day)	Mean Follow-up (Months)	Country	Relative Risk	95% CI[a]
					Non-fatal MI	CHD death or fatal MI + sudden death
Sacks (1995)	**Intervention:** Oil (2.9g per day EPA, 1.9g per day DHA), N=31 **Control:** Placebo, N=28	4.8	28	US	0.4 (0.0-5.1)	0.3 (0.0-7.4)[b]
Leng(1998)	**Intervention:** Oil (1.7g per day GLA, 0.3g per day EPA), N=60 **Control:** Sunflower oil	1.7	24	UK	0.7 (0.2-3.4)	RR not reported for fatal MI or sudden death

	N=60					
Nilsen (2001)	**Intervention:** Oil (1.2g per day EPA, 2.3g per day DHA), N=150 **Control:** Corn oil, N=150	3.5	18	Norway	RR not reported for non-fatal MI	1.0 0.4-2.7)
Marchioli (2002)	**Intervention:** Oil (0.3g per day EPA, 0.6g per day DHA), N=5,666 **Control:** No intervention	0.9	42	Italy	1.0	0.6

CHD, Coronary heart disease; CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GLA, gamma-linolenic acid; MI, myocardial infarction; RR, relative risk.

[a] Computed using SAS, version 8.2 for Windows (SAS Institute, Cary NC, 2001) PROC FREQ relrisk output option.
[b] Added 0.5 to each cell in the two-by-two table when one cell was empty in order to prevent the width of the confidence interval for the log-transformed relative risk from becoming infinitely wide.

Summary of Results:

Key Findings

- Analysis estimated that consuming small quantities of fish is associated with a 17% reduction in CHD mortality risk, with each additional serving per week associated with a further reduction in this risk of 3.9%
- Small quantities of fish consumption were associated with risk reductions in non-fatal MI risk by 27%, but additional fish consumption conferred no incremental benefits
- Assessment for individuals with pre-existing CHD was complicated by the limited RCT data. Four satisfactory RCTs were identified, which collectively provide three data points for each of the two end-points analyzed (CHD death and non-fatal MI). The assessment is further complicated by the fact that the n-3 PUFA intake rates investigated in the RCTs are far higher than levels corresponding to typical fish intake rates. Authors concluded that the information available is insufficient for the purpose of quantitatively analyzing the impact of fish consumption on CHD risk for individuals with pre-existing CHD
- Because of their design and the type of outcomes investigated, authors judged it to be inappropriate to use selected studies to quantify the extent to which mercury attenuates the relationships between fish consumption and CHD or MI.

Relationship Between Fish Consumption and CHD Event Relative Risk: Studies of Individuals With No Pre-existing CHD.

Analysis	Parameter	R2	CHD death		R2	Non-fatal MI	
			ΔRR	95%CI		ΔRR	95%CI
Linear regression	Intercept	23%	-0.17	-0.25 to -0.008	5.8%	-0.27	-0.34 to -0.21
	Servings per week		-0.039	-0.066 to -0.011		0.0083	-0.012 to 0.028
Quadratic regression	Intercept	25%	0.13	-0.26 to 0.002	45%	-0.19	-0.27 to -0.12
	Servings per week		-0.085	-0.20 to 0.03		-0.084	-0.15 to -0.015
	(Servings per week)^2		0.0076	-0.011 to 0.026		0.014	0.004 to 0.025

CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction; RR, relative risk.

Author Conclusion:

- The analysis estimated that consuming small quantities of fish is associated with a 17% reduction in CHD mortality risk, with each additional serving per week associated with a further reduction in this risk of 3.9%
- Small quantities of fish consumption were associated with risk reductions in non-fatal MI risk by 27%, but additional fish consumption conferred no incremental benefits.

Reviewer Comments:

Main Limitation

- *Authors did not specify which articles were initially selected for further review. Authors discuss articles initially selected from other evidence review (reference 19), but they did not describe how many of those articles were used to start the review and how many were selected from their own literature search*
- *In addition, authors did not describe in detail what methods they used to assess the quality of the data within each article included to conduct regression analysis.*

Research Design and Implementation Criteria Checklist: Review Articles

Relevance Questions

1.	Will the answer if true, have a direct bearing on the health of patients?	Yes
2.	Is the outcome or topic something that patients/clients/population groups would care about?	Yes
3.	Is the problem addressed in the review one that is relevant to nutrition or dietetics practice?	Yes
4.	Will the information, if true, require a change in practice?	Yes

Validity Questions

1.	Was the question for the review clearly focused and appropriate?	Yes
2.	Was the search strategy used to locate relevant studies comprehensive? Were the databases searched and the search termsused described?	Yes
3.	Were explicit methods used to select studies to include in the review? Were inclusion/exclusion criteria specified and appropriate? Were selection methods unbiased?	Yes
4.	Was there an appraisal of the quality and validity of studies included in the review? Were appraisal methods specified, appropriate, and reproducible?	Yes
5.	Were specific treatments/interventions/exposures described? Were treatments similar enough to be combined?	Yes
6.	Was the outcome of interest clearly indicated? Were other potential harms and benefits considered?	Yes
7.	Were processes for data abstraction, synthesis, and analysis described? Were they applied consistently across studies and groups? Was there appropriate use of qualitative and/or quantitative synthesis? Was variation in findings among studies analyzed? Were heterogeneity issued considered? If data from studies were aggregated for meta-analysis, was the procedure described?	Yes
8.	Are the results clearly presented in narrative and/or quantitative terms? If summary statistics are used, are levels of significance and/or confidence intervals included?	Yes
9.	Are conclusions supported by results with biases and limitations taken into consideration? Are limitations of the review identified and discussed?	Yes
10.	Was bias due to the review's funding or sponsorship unlikely?	Yes